Attachment #1
Specific Comments

SPECIFIC COMMENTS

Lines 43-47
The proposed text in the draft guidance is the following:

WARNING: CIGARETTE SMOKING

Combined oral contraceptives (OCs) are not recommended for women who are over 35 years old and smoke. Cigarette smoking increases the risk of serious cardiovascular side effects from OC use. The risk increases with age and with the number of cigarettes smoked.

We recommend the inclusion of some qualifying information regarding the risks as they relate to the number of cigarettes smoked. This information is important for clinicians when making prescribing decisions. The following revision is therefore submitted for your consideration:

WARNING: CIGARETTE SMOKING
Combined oral contraceptives (OCs) are not recommended for women who are over 35 years old and smoke. Cigarette smoking increases the risk of serious cardiovascular side effects from OC use. The risk increases with age (especially after age 35) and with heavy smoking (especially 15 or more cigarettes per day).

Line 80
The proposed labeling presented in the draft guidance is the following:

(Name of OC) is indicated for use by women to lower the risk of becoming pregnant.

It is proposed that this language be replaced with the following language which is more comprehensible from a patient perspective:

(Name of OC) is indicated for use by women to help prevent pregnancy.

Lines 82-92
The proposed labeling presently in the draft guidance is the following:

Pregnancy rates from clinical trials should be placed here.
In clinical trials of (*insert name of OC here*), about (*insert whole number here*) out of 100 women became pregnant during the first year of use. The effectiveness of any OC depends on correct and consistent use, and factors that affect ability to conceive, including age and frequency of intercourse.

The following table shows estimates of the number of women who become pregnant during the first year of use, based mainly on clinical trial data, for various birth control methods.

Approximate Percentage of Women Who Become Pregnant During the First Year of Use of a Birth Control Method*	
METHOD	PREGNANCIES PER 100 WOMEN PER YEAR
estrogen/progestin injection levonorgestrel implants levonorgestrel IUD and copper IUD medroxyprogesterone acetate injection sterilization	Fewer than 1
estrogen/progestin contraceptive products: • pills • skin patch • vaginal ring	1
progestin-only pills	2
condom (male) diaphragm	15
Spermicides	25 or more

*The estimates for drugs, condoms, diaphragms, and IUDs are derived from clinical trial data reviewed by the Food and Drug Administration. The estimates for sterilization and spermicides come from the medical literature.

We recommend the use of the "Percentage Of Women Experiencing An Unintended Pregnancy During The First Year Of Typical Use And The First Year Of Perfect Use Of Contraception And The Percentage Continuing Use At The End Of The First Year. United States." table (henceforth referred to as the Trussell Table) used in the previous draft guidance for following reasons:

- The table provides failure rates for a wide range of contraceptive methods and also allows the practitioner to evaluate rates versus chance or no method.
- The table includes typical failure rates which are based on population data as well as perfect use failure rates which provide clinicians more information for patient counseling regarding efficacy.

Additionally, we have the following questions regarding the use of the proposed table:

- What is source for data in proposed table?
- Have data from these trials been submitted to the agency for review?
- Is this data available to the public?

The following revision is therefore submitted for your consideration in place of the table proposed in the 2004 guidance document:

Table 2: Percentage Of Women Experiencing An Unintended Pregnancy During The First Year Of Typical Use And The First Year Of Perfect Use Of Contraception And The Percentage Continuing Use At The End Of The First Year. United States.

	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	Typical Use [1] (2)	Perfect Use[2] (3)	(4)
Chance[4]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[6]		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptives Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[9]

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.[10]

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowel D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

[1] Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[2] Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[3] Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

[4] The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[5] Foams, creams, gels, vaginal suppositories, and vaginal film.

[6] Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

[7] With spermicidal cream or jelly.

[8] Without spermicides.

[9] The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 4 yellow pills).

[10] However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Additionally, use of the latest revision of the Trussell table that will be included in the 18th edition of Contraceptive Technology is highly recommended. This is expected to include newer methods such as the contraceptive patch and the vaginal ring. We recommend using this newer version of the Trussell table in place of the above recommended version when it becomes available.

Line 108

The proposed labeling presently in the draft guidance is the following:

- Liver tumors, now or in the past, or liver disease

We believe that this wording is not specific and does not distinguish tumors from other liver masses and enlargements. In addition, the qualifying language of "abnormal liver function" is pertinent to prescribing decisions and should be included. Without it, listing liver disease alone as a contraindication may be unnecessarily restrictive. The following revision is therefore submitted for your consideration:

- ***Liver tumors, now or in the past***

- ***Acute or chronic liver disease, with abnormal liver function***

Line 110
The proposed labeling presently in the draft guidance is the following:

- Any condition predisposing to thrombotic diseases

We believe the language is vague and may be too general and therefore not useful to prescribing clinicians. We therefore propose the following more specific revision:

- ***Major surgery with prolonged immobilization***

Line 111
The proposed labeling presently in the draft guidance is the following:

- Thrombophlebitis or pulmonary embolism, now or in the past

We believe that deep vein thrombosis provides a more specific recommendation and that superficial thrombophlebitis should not be a contraindication. We therefore propose the following revision for your consideration:

- ***Deep vein thrombophlebitis or pulmonary embolism, now or in the past***

Line 112
The proposed labeling presently in the draft guidance is the following:

- Cerebrovascular disease

The following revision is submitted for your consideration:

- ***Cerebrovascular disease, now or in the past***

Line 113
The proposed labeling presently in the draft guidance is the following:

- Coronary artery disease

The following revision is submitted for your consideration:

- ***Coronary artery disease, now or in the past***

Line 115
The proposed labeling presently in the draft guidance is the following:

- Congenital hypercoagulopathies

We recommend deleting this based on the discussion of factor V leiden mutation and other hereditary coagulation disorders in the Warnings section (lines 169-170). In addition, such a contraindication may require screening of all OC candidates by the clinician – which many experts have argued to be of limited value for OC users. Sources: Human Reproduction 2000;15(2):485-492.; Pathophysiol Haemost Thromb. 2002 Sep-Dec;32(5-6):315-7.; Curr Opin Pediatr. 2002 Aug;14(4):370-8.

Line 117
The proposed labeling presently in the draft guidance is the following:

- Uncontrolled hypertension

We recommend specification of the nature of the uncontrolled hypertension as severe – which is defined as persistent systolic values of ≥160 or persistent diastolic values of ≥100 mm Hg. This is based on the following source: World Health Organization: Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use. 2nd Ed. Geneva, Switzerland. The following revision is therefore submitted for your consideration:

- ***Uncontrolled, severe hypertension (persistent systolic values of ≥160 or persistent diastolic values of ≥100 mm Hg)***

Line 119
The proposed labeling presently in the draft guidance is the following:

- Smoking and over age 35

Data support a contraindication with both an age and a number of cigarettes smoked threshold (Source: World Health Organization: Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use. 2nd Ed. Geneva, Switzerland). Therefore, we recommend the inclusion of some qualifying information regarding this risk as it relates to the number of cigarettes smoked. The following revision is therefore submitted for your consideration:

- ***Smoking (≥15 cigarettes a day) and age over 35***

We also recommend retaining the following contraindication from the 1994 Guideline Document because we are aware of no convincing evidence of the safety of OC use for women with cancer of the endometrium:

- ***Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia***

Additionally, we again recommend adding the following contraindication because a history of cholestatic jaundice in pregnancy or prior OC use has been associated with an increased incidence of cholestatic jaundice with subsequent pill use:

- ***Cholestatic jaundice of pregnancy or jaundice with prior pill use***

Lines 107-121
In summation, we propose the following list of contraindications in the following order (based on severity):

- ***Smoking (≥15 cigarettes a day) and age over 35***
- ***Deep vein thrombophlebitis or pulmonary embolism, now or in the past***
- ***Cerebrovascular disease, now or in the past***
- ***Coronary artery disease, now or in the past***
- ***Thrombogenic valvular or thrombogenic rhythm diseases of the heart***
- ***Uncontrolled, severe hypertension (persistent systolic values of ≥160 or persistent diastolic values of ≥100 mm Hg)***
- ***Diabetes with vascular disease***
- ***Migraines with focal neurologic symptoms***
- ***Major surgery with prolonged immobilization***
- ***Breast cancer or other hormone-sensitive cancer, now or in the past***
- ***Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia***
- ***Undiagnosed abnormal genital bleeding***
- ***Cholestatic jaundice of pregnancy or jaundice with prior pill use***
- ***Liver tumors, now or in the past***
- ***Acute or chronic liver disease, with abnormal liver function***
- ***Pregnancy***
- ***Allergy to any components of this drug product***

Line 125
We recommend inserting a new paragraph to help qualify much of the information contained within the labeling. This paragraph is included in the current OC class labeling. The following revision is therefore submitted for your consideration:

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogen and progestins than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestins remains to be determined.

Lines 131-134
The proposed labeling presently in the draft guidance is the following:

Minimizing exposure to estrogen and progestin reduces the risk of thrombotic events. For any particular estrogen/progestin combination, the recommended dosage regimen is

that which contains the least amount of estrogen and progestin that is compatible with a low pregnancy rate and the medical needs of the individual patient.

The following revision is submitted for your consideration:

Minimizing exposure to estrogen and progestin may reduce the risk of thrombotic events. For any particular estrogen/progestin combination, the recommended dosage regimen is that which contains the least amount of estrogen and progestin that is compatible with a low pregnancy rate and the medical needs (including tolerability and cycle control) of the individual patient.

Lines 146-147
The proposed labeling presently in the draft guidance is the following:

Observational studies suggest an increased risk of superficial thrombophlebitis, deep vein thrombosis, and pulmonary embolism in OC users compared to non-OC users.

We recommend deleting superficial thrombophlebitis. Additionally, we recommend including newer available references within the thromboembolism section as a whole (see list provided). The following revision is therefore submitted for your consideration:

Observational studies suggest an increased risk of thrombophlebitis, deep vein thrombosis, and pulmonary embolism in OC users compared to non-OC users.

Lines 180-184
The proposed labeling presently in the draft guidance is the following:

An increased risk of myocardial infarction is attributed to OC use. This risk is mainly in women with underlying risk factors for coronary artery disease such as smoking, hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current OC users compared to nonusers is estimated to be two to six.[21,22,23,24,25,26,27] The risk is very low under the age of 30.

The references cited are from 1975 to 1986. We recommend including newer references regarding this issue (see list provided).

Lines 199-200
The proposed labeling presently in the draft guidance is the following:

In observational studies, OCs appear to increase the risk of strokes, although, in general, the risk is greatest among hypertensive women over age 35 who also smoke.[31,32,33]

The references cited are from 1973 to 1979. We recommend including newer references regarding this issue (see list provided).

Lines 218-220
The proposed labeling presently in the draft guidance is the following:

There is substantial evidence that OCs do not increase the incidence of breast cancer.[41,42] Although some past studies have suggested that OCs might increase the incidence of breast cancer, more recent and thorough studies have not confirmed such findings.

Although newer and more favorable data has become available regarding the risk of breast cancer associated with oral contraceptive use, we feel it is important to continue to acknowledge previous published literature which has highlighted that the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. Therefore, we recommend the following revision for consideration:

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after discontinuation of combination oral contraceptives and by 10 years after cessation the increased risk disappears. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally sensitive tumor.[41]

Lines 260-261
The proposed labeling presently in the draft guidance is the following:

Women with uncontrolled hypertension or hypertension with vascular disease should not use OCs.

We recommend specification of the nature of the uncontrolled hypertension as severe – which is defined as persistent systolic values of ≥160 or persistent diastolic values of ≥100 mm Hg (per WHO reference cited previously). The following revision is therefore submitted for your consideration:

Women with severe, uncontrolled hypertension (persistent systolic values of ≥160 or persistent diastolic values of ≥100 mm Hg) or hypertension with vascular disease should not use OCs.

Line 282
We recommend adding the following statement after line 281 regarding amenorrhea risk once an oral contraceptive is discontinued:

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

Line 284
We recommend including the following statement regarding ectopic pregnancy as we are not currently aware of data to support the removal of this warning:

Ectopic pregnancy as well as intrauterine pregnancy may occur in contraceptive failures.

Lines 290-292
The proposed labeling presently in the draft guidance is the following:

Women who are using oral contraceptives should have an annual history and physical examination, including special reference to blood pressure, breasts, abdomen and pelvic organs, as well as cervical cytology and relevant laboratory tests.

A recent review, that included policy statements from major organizations such as the World Health Organization (WHO), the International Planned Parenthood Federation, the American College of Obstetricians and Gynecologists, and Planned Parenthood Federation of America, concluded the following: "Clinical breast and pelvic examinations are commonly accepted practices prior to provision of hormonal contraception. Such examinations, however, may reduce access to highly effective contraceptive methods, and may therefore increase women's overall health risks. Consensus developed during the last decade supports a change in practice: hormonal contraception can safely be provided based on careful review of medical history and blood pressure measurement." Source: *JAMA.* 2001;285:2232-2239. The following revision is therefore submitted for your consideration:

Women who are using oral contraceptives should have an annual history and physical examination, including special reference to blood pressure, breasts, abdomen and pelvic organs, as well as cervical cytology and relevant laboratory tests. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician.

Lines 311-313
The proposed labeling presently in the draft guidance is the following:

Some examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamezepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

Phenylbutazone is no longer approved, and thus not marketed, for any human use in the United States. Source: http://www.fda.gov/cvm/index/updates/buteup.htm. Additionally, the paragraph has been expanded to include more specific information on the metabolism of hormonal OCs. The following revision is therefore submitted for your consideration:

Some examples include rifampin, barbiturates, phenytoin, carbamezepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. The metabolism of hormonal contraceptives may be influenced by various drugs. Of potential clinical importance are drugs that

cause the induction of enzymes that are responsible for the degradation of estrogens and progestins, and drugs that interrupt entero-hepatic recirculation of estrogen (e.g. certain antibiotics). The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Although the literature is mixed, some studies suggest possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline.

Lines 378-381
The proposed labeling presently in the draft guidance is the following:

There appears to be little or no increased risk of birth defects in women who have used OCs inadvertently during early pregnancy.[73,74] *However, if any component of the drug product is associated with birth defects, add a statement about the types of defects, estimated frequency, the associated doses, and the gestational age of exposure, if known.*

We recommended reiterating the fact that oral contraceptives are contraindicated in pregnant women. The following additional verbiage is therefore submitted for your consideration:

Oral contraceptives should not be used by women who are pregnant (See CONTRAINDICATIONS section). There appears to be little or no increased risk of birth defects in women who have used OCs inadvertently during early pregnancy.[73,74] However, if any component of the drug product is associated with birth defects, add a statement about the types of defects, estimated frequency, the associated doses, and the gestational age of exposure, if known.

Lines 402-423
The proposed labeling presently in the draft guidance is the following:

ADVERSE EXPERIENCES

The most serious adverse reactions associated with the use of OCs are in the WARNINGS and PRECAUTIONS sections.

Other side effects commonly reported by OC users are:

- Nausea
- Breast tenderness
- Headaches

The following adverse reactions may occur less frequently:

- Acne
- Decreased libido
- Dizziness
- Fluid retention

- Increased cervical ectopia
- Melasma
- Mood changes and depression
- Ocular effects, including decreased tolerability to contact lenses
- Vaginal candidiasis
- Vomiting and other gastrointestinal symptoms (e.g., bloating)
- Weight changes

The proposed list does not provide a comprehensive list of all adverse reactions which have reported with OCs. The following revision is therefore submitted for your consideration:

ADVERSE REACTIONS

The most serious adverse reactions associated with the use of OCs are in the WARNINGS and PRECAUTIONS sections.

The most common side effects reported by OC users are:

- ***Nausea***
- ***Breast tenderness***
- ***Headaches***
- ***Breakthrough bleeding and/or spotting***

The following adverse reactions have also been reported in patients receiving oral contraceptives and are believe to be drug related:

- ***Vomiting***
- ***Gastrointestinal symptoms (such as abdominal cramps and bloating)***
- ***Change in menstrual flow***
- ***Amenorrhea***
- ***Edema***
- ***Melasma which may persist***
- ***Breast changes: enlargement, secretion***
- ***Change in weight (increase or decrease)***
- ***Change in cervical erosion and secretion***
- ***Diminution in lactation when given immediately postpartum***
- ***Cholestatic jaundice***
- ***Migraine***
- ***Rash (allergic)***
- ***Mental depression***
- ***Reduced tolerance to carbohydrates***
- ***Vaginal candidiasis***
- ***Change in corneal curvature (steepening)***
- ***Intolerance to contact lenses***

The following adverse reactions have also been reported in patients receiving oral contraceptives and a cause and effect association has neither been confirmed nor refuted:

- ***Temporary infertility after discontinuation of treatment***
- ***Pre-menstrual syndrome***
- ***Cataracts***
- ***Changes in appetite***
- ***Cystitis-like syndrome***
- ***Nervousness***
- ***Dizziness***
- ***Hirsutism***
- ***Loss of scalp hair***
- ***Erythema multiforme***
- ***Erythema nodosum***
- ***Hemorrhagic eruption***
- ***Vaginitis***
- ***Porphyria***
- ***Impaired renal function***
- ***Hemolytic uremic syndrome***
- ***Acne***
- ***Changes in libido***
- ***Colitis***
- ***Budd-Chiari Syndrome***

Lines 433-438
The proposed labeling presently in the draft guidance is the following:

Possible benefits associated with OC use beyond lowering of risk of becoming pregnant include the following effects on menses:

- More regular
- Less blood loss
- Less dysmenorrhea

We recommend including the entire list of non-contraceptive health benefits related to oral contraceptives. These are well-established findings from epidemiological studies that allow the clinician and patient to appropriately balance the risk and benefits of oral contraceptives. The following revision is therefore submitted for your consideration:

The following possible benefits associated with OC use beyond helping to prevent pregnancy are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses:

- ***More regular***
- ***Less blood loss***
- ***Less dysmenorrhea***

Effects related to inhibition of ovulation:

- ***Decreased incidence of functional ovarian cysts***
- ***Decreased incidence of ectopic pregnancies***

Other effects:

- ***Decreased incidence of fibroadenomas and fibrocystic disease of the breast***
- ***Decreased incidence of acute pelvic inflammatory disease***
- ***Decreased incidence of endometrial cancer***
- ***Decreased incidence of ovarian cancer***

Lines 466-468
The proposed labeling presently in the draft guidance is the following:

REFERENCES

Supplied upon request.

We recommend including a listing of references in the physician labeling as included in the current labeling. This is a valuable resource for the clinician and also helps provide perspective on source and year of publication of the information provided.

Lines 476-480
The proposed labeling presently in the draft guidance is the following:

WARNING: CIGARETTE SMOKING

Do not use (*OC name*) if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious side effects from birth control pills, including death from heart attack, blood clots, or stroke. This risk increases with age and the number of cigarettes you smoke.

We recommend the inclusion of some qualifying information regarding the risks as they relate to the number of cigarettes smoked. This information is important for clinicians when making prescribing decisions. The following revision is therefore submitted for your consideration:

WARNING: CIGARETTE SMOKING

Combined oral contraceptives (OCs) are not recommended for women who are over 35 years old and smoke. Cigarette smoking increases your risk of serious side effects from birth control pills, including death from heart attack, blood clots, or stroke. This risk increases with age (especially after age 35) and the number of cigarettes you smoke (especially 15 or more cigarettes per day).

Lines 503-506

The proposed labeling presently in the draft guidance is the following:

The following table shows how the birth control pill compares with some other methods of birth control. The numbers are estimates of the number of women out of 100 women who become pregnant in 1 year of use.

Fewer Pregnancies

Number of women out of 100 who become pregnant in 1 year	Birth Control Method
Fewer than 1	Sterilization, implants, intrauterine device (IUD), injection
1	**Birth control pills** , skin patch, vaginal ring with hormones
15	Condom, diaphragm
25 or more	Spermicides

More Pregnancies

We recommend deleting the above table and using data adapted from the Trussell Table as done in current class OC labeling. This list provides typical failure rates for other methods of birth control during the first year of use.

Additionally, we have the following questions regarding the use of the proposed table:

- What is source for data in proposed table?
- Have data from these trials been submitted to the agency for review?
- Is this data available to the public?

The following revision is therefore submitted for your consideration in place of the table proposed in the 2004 guidance document:

Typical failure rates for other methods of birth control during the first year of use are as follows:
Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 20%
Spermicides alone: 26%
Vaginal sponge: 20 to 40%
Female sterilization: <1%
Male sterilization: <1%
Cervical Cap with spermicide: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

Additionally, the latest revision of the Trussell table will be included in the 18th edition of Contraceptive Technology. This is expected to include newer methods such as the contraceptive patch and the vaginal ring. We recommended including the failure rates for these methods in the list above when they become available.

Lines 521-523
The proposed labeling presently in the draft guidance is the following:

In the Brand X clinical trials, women were told to start the first pack on day 1 of their menstrual periods. Brand X instructions do not include Sunday Start instructions because Sunday Start was not studied in the clinical trials.

OC labeling has historically provided instructions for both Sunday start and day 1 start methods. In addition, both Sunday start as well as day 1 start have been tested in the clinical setting. The Sunday start and day 1 start methods have demonstrated safety and efficacy in both clinical trial settings and every day use. Supplying instructions for only one starting method will limit dosing and administration options from the patient perspective. In addition, guidelines from the WHO are more liberal in relation to OC start date than current class labeling. The following revision is therefore submitted for your consideration:

Include both Sunday Start and Day 1 Start instructions as listed currently in class OC labeling.

Lines 544-545
The proposed labeling presently in the draft guidance is the following:

Use a backup birth control method such as condoms or spermicide for 7 days after you miss any of the active *(insert color here)* pills.

We realize the value in simplifying the language regarding missed pills in the class OC labeling. However, OC class labeling has historically recommended backup contraception for missed pills only when 2 or more pills are missed. We feel this recommendation remains to be appropriate and rational and are not aware of any data that would prove otherwise. Published research has estimated that a significant percentage of patients (up to 50% from self-reports and 80% from electronic monitoring) miss one pill per oral contraceptive cycle (Fox MC et al. Contraception 2003;68:365-371). In light of the lack of clinical evidence to support the use of back up contraception after just one missed active pill and the high percentage of patients who miss just one pill, such a recommendation may not be practical and would be overly burdensome from the patient perspective. Therefore, the following revision is therefore submitted for your consideration:

Use a back up birth control method such as condoms or spermicide for 7 days after you miss two or more consecutive active (insert color here) pills.

Lines 571-588
The proposed labeling presently in the draft guidance is the following:

- Ever had breast cancer or any cancer that is sensitive to hormones
- Liver disease, including liver tumors
- Unexplained bleeding from your vagina
- Ever had blood clots in your arms, legs, or lungs
- Ever had a stroke
- Ever had a heart attack or chest pains
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine can't control
- Diabetes with kidney, eye, or blood vessel damage
- Severe migraine headaches

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are pregnant
- Are allergic to anything in *(OC)*

To ensure consistency with physician labeling and to maintain user friendly language, we recommend including suggested edits to physician labeling into patient labeling. The following revision is therefore submitted for your consideration:

- ***Smoking (≥15 cigarettes a day) and age over 35***
- ***Ever had a blood clot in the deep veins of your legs (deep vein thrombophlebitis), your arms, or lungs (pulmonary embolism)***
- ***Ever had a stroke***
- ***Ever had a heart attack or chest pain (angina pectoris)***
- ***Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart***
- ***Severe high blood pressure that medicine can't control***
- ***Diabetes with kidney, eye, or blood vessel damage***
- ***Migraine headaches with focal neurologic symptoms***
- ***Need for a prolonged period of bed rest following major surgery***
- ***Ever had breast cancer***
- ***Known or suspected cancer of the lining of the uterus or any cancer that is sensitive to hormones***
- ***Vaginal bleeding of unknown cause (until your doctor reaches a diagnosis)***
- ***Yellowing of the whites of your eye or of the skin (jaundice) during pregnancy or during previous use of hormonal contraceptives***
- ***Liver tumor (benign or cancerous)***
- ***Liver disease with abnormal liver function blood tests***
- ***Known or suspected pregnancy***
- ***An allergic reaction to the components of (list name of OC here)***

Lines 594-595
The proposed labeling presently in the draft guidance is the following:

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy, also called cholestasis of pregnancy.

We recommend including this in the listing of contraindications as recommended for physician labeling (also included in patient labeling) (see above lines 571-588).

Lines 633-653
The proposed labeling presently in the draft guidance is the following:

WHAT ARE COMMON SIDE EFFECTS OF BIRTH CONTROL PILLS?

The most common side effects of birth control pills are:

- Nausea
- Breast tenderness
- Headache

- Bleeding between menstrual periods

These side effects are usually mild and may disappear with time.

Less common side effects are:

- Bloating or fluid retention.
- Darkening of the skin, especially on the face. This problem may be related to the darkening of the skin that sometimes happens during pregnancy.
- High blood sugar, especially in women who already have diabetes.
- High triglycerides (high fat levels in the blood).
- Depression, especially if you have had depression in the past. Call your health care provider immediately if you have any thoughts of harming yourself.
- Weight changes.

We recommend listing side effects, to be consistent with the final physician labeling. Therefore, the following revision is proposed for your consideration:

The most common side effects of birth control pills are:

- ***Nausea***
- ***Breast tenderness***
- ***Headache***
- ***Bleeding between menstrual periods***

These side effects are usually mild and may disappear with time.

Some other side effects that have been reported with birth control pills and are believed to be drug related include:

- ***Vomiting***
- ***Abdominal cramping and bloating***
- ***Spotting***
- ***Change in menstrual flow***
- ***The absence of one or more menstrual periods***
- ***Bloating or fluid retention***
- ***Swelling of the feet, legs, hands, or face***
- ***Darkening of the skin, especially on the face***
- ***Breast changes, such as an increase in size or leakage of fluid from the nipples***
- ***Weight changes***
- ***Change in the appearance of the cervix or discharge from the vagina***
- ***Decrease in breast milk production when used immediately after birth***
- ***Yellowing of the skin and/or eyes***
- ***Migraine headache***
- ***Allergic rash***

- ***Depression, especially if you have had depression in the past. Call your healthcare professional immediately if you have any thoughts of harming yourself.***
- ***High blood sugars, especially in women who already have diabetes***
- ***High triglycerides (high fat levels in the blood)***
- ***Vaginal yeast infections***
- ***Change in the shape of the eye making use of contact lenses difficult and/or uncomfortable***

The following additional side effects have also been reported among users of birth control pills, however it is not clear whether these side effects are caused by birth control pills:

- ***Difficulty getting pregnant after stopping the pill***
- ***Pre-menstrual syndrome***
- ***Clouding of the eye lenses making it difficult to see***
- ***Changes in appetite***
- ***Increased frequency and burning with urination***
- ***Nervousness***
- ***Dizziness***
- ***Increased body hair***
- ***Thinning of scalp hair***
- ***A reddening of the skin or rash called erythema multiforme***
- ***An abnormal flushing of the skin with painful swelling called erythema nodosum***
- ***Red spots on the skin***
- ***Irritation of the vagina***
- ***Porphyria (a type of blood disorder)***
- ***Decreased function of the kidneys***
- ***Hemolytic uremic syndrome***
- ***Acne***
- ***Changes in sex drive***
- ***Colitis***
- ***Budd-Chiari Syndrome (a type of liver disorder)***

Lines 655-656
The proposed labeling presently in the draft guidance is the following:

This is not a complete list of possible side effects. Talk to your health care provider if you develop any side effects that concern you.

We recommend adding the following sentence from the physician labeling to ensure consistency:

It is not always clear whether these side effects are caused by OCs and, if so, whether the estrogen and/or the progestin is responsible. This is not a complete list of possible side effects. Talk to your health care professional if you develop any side effects that concern you.

Lines 673-677
The proposed labeling presently in the draft guidance is the following:

A few women who take birth control pills may get:

- Rare cancerous or noncancerous liver tumors
- Gallbladder problems
- High blood pressure

We recommend revising this sentence to emphasize the rareness of these side effects – in particular the liver tumors and gallbladder problems. The following revision is therefore submitted for your consideration:

Medical problems that may occur infrequently in women who take birth control pills include:

- ***Rare cancerous or noncancerous liver tumors***
- ***Gallbladder problems***
- ***High blood pressure***

Lines 690-694
The proposed labeling presently in the draft guidance is the following:

DO BIRTH CONTROL PILLS CAUSE CANCER?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Although newer and more favorable data has become available regarding the risk of breast cancer associated with oral contraceptive use, we feel it is important to continue to acknowledge previous published literature which has highlighted that the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. This is especially important for counseling purposes in the patient labeling. Therefore, we recommend the following revision for consideration:

DO BIRTH CONTROL PILLS CAUSE CANCER?

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. Women who

currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually hormone-sensitive tumor.

Lines 707-713
The proposed labeling presently in the draft guidance is the following:

ARE THERE OTHER BENEFITS OF THE BIRTH CONTROL PILL?

Yes. Your menstrual periods may become:

- More regular
- Lighter
- Less painful

We recommend including the entire list of non-contraceptive health benefits that are consistent with the physician labeling. The following revision is therefore submitted for your consideration:

ARE THERE OTHER BENEFITS OF THE BIRTH CONTROL PILL?

Yes. Your menstrual periods may become:

- ***More regular***
- ***Lighter***
- ***Less painful***

The following conditions may occur less frequently:

- ***Cysts in the ovaries***
- ***Ectopic (tubal) pregnancy***
- ***Non-cancerous cysts or lumps in the breast***
- ***Acute pelvic inflammatory disease (infection of the tubes and ovaries)***

Oral contraceptive use may provide some protection against developing two forms of cancer:

- ***Cancer of the ovaries***
- ***Cancer of the lining of the uterus***